Utjecaj kompleksacije piroksikama s ciklodekstrinima na oblikovanje gela

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Source / Izvornik: **Acta Pharmaceutica, 2005, 55, 223 - 236**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:163:266337

Acta Pharm. 55 (2005) 223–236 Original research paper

Influence of cyclodextrin complexation on piroxicam gel formulations

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The aim of this work was to evaluate the role of cyclodextrins in topical drug formulations. Solid piroxicam (PX) complexes with β-cyclodextrin (β-CD) and randomly methylated β-cyclodextrin (RAMEB) were prepared by freeze-drying and characterized using differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), Fourier transform infrared spectroscopy (FTIR) and near infrared spectroscopy (NIR). A physical mixture of PX and cyclodextrins was characterized by enhanced dissolution properties compared to the dissolution profile of the pure drug due to *in situ* complex formation. Formation of the PX-cyclodextrin inclusion complex additionally improved the drug dissolution properties. Influence of CDs on drug permeation from the water dispersion and the prepared hydroxypropyl methylcellulose (HPMC) gels was investigated. Permeation of the drug involved three consecutive processes: dissolution of the solid phase, diffusion across the swollen polymer matrix and drug permeation through the membrane. Complexation increased PX diffusion by increasing the amount of diffusible species in the donor phase. Slower drug diffusion through the HPMC matrix was the rate limiting step in the overall diffusion process. Possible interaction between the hydrophilic polymer and cyclodextrin may result in physicochemical changes, especially in a change of rheological parameters.

Received March 22, 2005
Accepted September 9, 2005

Keywords: piroxicam, hydroxypropyl methylcellulose, cyclodextrin, topical delivery

Piroxicam (PX) is a potent non-steroidal, anti-inflammatory agent used in treatment of rheumatoid arthritis, osteoarthritis, traumatic contusions and different regional inflammatory disorders such as muscle pain (1). It is well absorbed following oral administration; however, its use has been associated with a number of gastro-intestinal disorders. Because of these side effects connected with the oral use of PX, development of various topical dosage forms of the drug was proposed. Owing to its physiochemical characteristics, PX is suitable for topical delivery. Among the different NSAIDs, PX shows a relatively high percentage of unionized moiety at the skin pH value. The drug *log P*

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value is close to the optimum value of about 2.5 indicated for NSAIDs while its solubility in the stratum corneum is low. Since piroxicam has a half-life of 40.8 h, it is slowly eliminated, resulting in higher blood plasma levels (2). The PX solubility in water is low. Molecular complexation of PX with β-cyclodextrin improved drug solubility, and therefore it could be expected to hasten PX absorption, resulting in a faster onset of action (3).

Cyclodextrins (CDs) have been reported to modify transdermal drug penetration of many compounds by complexation. If the drug is loaded in the vehicle in a concentration above saturation, CDs can accelerate its release by enhancing the proportion of diffusible species. When the drug proportion in the vehicle is below the solubility limit, complexation reduces the concentration of free drug molecules that could penetrate through the skin, thereby prolonging drug release (4).

Because of their relatively high molecular mass and outer surface hydration, under normal conditions CDs and their complexes will penetrate biological membranes with considerable difficulties (5). CDs act as true carriers by keeping the poorly soluble drug molecules in solution and delivering them to the skin surface, from where they penetrate into the skin barrier (5, 6).

Percutaneous penetration involves drug dissolution in the vehicle, diffusion of the solubilized drug from the vehicle to the surface of the skin, and drug penetration through the skin layers. Selection of the appropriate vehicle and modification of drug characteristics may improve penetration. Comparing the influence of the vehicle on PX release, it seems that HPMC gels are the vehicle of choice for fast release and high anti-inflammatory effects of PX after topical application (7, 8). Okuyama *et al.* (9) have shown that the transdermal PX bioavailability increased with an increase of the cataplasm pH value up to 6.5, and afterwards remained constant. PX solubility is higher at higher pH values, but the drug is in the ionized form and cannot penetrate the skin barrier. They have also demonstrated the positive influence of cosolvents such as propylene glycol on PX penetration in the skin, muscles and plasma.

Doliwa *et al.* (10) investigated the influence of HP-β-CD on *in vitro* PX permeation and skin retention. The flux of the drug increased 2-fold in the presence of HP-β-CD, but the skin retention of the drug remained similar to that in the control gel. They used propylene glycol as cosolvent and the presence of propylene glycol reduced the PX-HP-β-CD complex stability constant 28.7 times. It seems that propylene glycol caused displacement of the PX molecule from the complex, reducing the positive effect of HP-β-CD on PX solubility, and therefore minimized the positive effect of CDs on transdermal penetration.

In this study, we have prepared and characterized solid PX complexes with β-CD and RAMEB. The influence of complexation on the properties of HPMC hydrogels and *in vitro* drug release was investigated. Hydrogels contained dispersed PX, PX-β-CD and PX-RAMEB complexes, without any cosolvents.

EXPERIMENTAL

Materials

Piroxicam was kindly donated by Belupo (Croatia). β-cyclodextrin and randomly methylated β-cyclodextrin with an average substitution degree of 1.8 per anhydroglucose unit were used as received (Wacker, Chemie GmbH, Germany). Hydroxypropyl methyl-

cellulose (HPMC), Metolose®, viscosity 4000 mPa s (2% aqueous solution), was obtained from Shin-Etsu Chemical Co. Ltd., Japan. All other materials and solvents used were of analytical grade.

Preparation of solid systems

Physical mixtures and lyophilized complexes were prepared in 1:1 PX: CD molar ratio, based on the results of the solubility studies (11).

To prepare physical mixtures of the drug and both CDs, weighed PX and β-CD or RAMEB were passed through 0.5-mm mesh sieves and were homogeneously blended in a Turbula T2C mixer (Willy A Bachofen AG, Switzerland) for 10 min.

To prepare freeze-dried complexes, PX was added to β-CD or RAMEB water solution and stirred at 600 rpm until a stabile suspension was formed. Then PX was dissolved by addition of ammonium hydroxide and the solution was stirred for the following 24 hours at ambient temperature to attain complexation equilibrium. Prepared solutions were frozen and lyophilized in a freeze dryer to obtain solid complexes (Freeze Dryer Alpha 1–4, M. Christ, Gefriertrocknungslangen GmbH, Germany).

Solid systems characterisation

Differential scanning calorimety. – DSC thermograms of the drug, cyclodextrins, physical mixtures and freeze-dried complexes were recorded on a Perkin Elmer DSC 7, USA. The instrument was calibrated with indium and zinc prior to analyzing the samples under nitrogen. All accurately weighed samples (2–5 mg) were placed into sealed aluminium pans, and scanned at a heating rate of 10 °C min^{-1} over the temperature range of 30–250 °C.

X-ray powder diffractometry. – The XRPD patterns were recorded using a Phillips X'pert Pro powder diffractometer (The Netherlands) at 40 mV, 45 KV, with monochromatized CuKα radiation (λ = 1.54056 Å). The samples were scanned at room temperature in continuous scan mode over the range 3–40° with step size of 0.01671 2θ and counting time of 19.95 s. Data were analyzed using the software package X'pert Plus, version 1.3e.

Fourier transform infrared spectroscopy. – The FTIR spectra of the free drug, cyclodextrins, physical mixtures and freeze-dried complexes were recorded with a Perkin Elmer spectrum GX spectrometer. The samples were prepared by the potassium bromide disc method and scanned for absorbance in the 4000–370 cm^{-1} region.

Near infrared spectroscopy. – The NIR spectra of the free drug, cyclodextrins, physical mixtures and freeze-dried complexes were measured using a Bruker NIR Multi Purpose Analyser (Germany). The spectra were recorded in a diffuse reflectance mode using an integrating sphere for collecting reflecting beams. The measurements were carried out in triplicate over the range 4000–12000 cm^{-1}, with a resolution of 8 cm^{-1}. The spectra were averaged over 32 scans. The system was run via the software OPUS for acquisition and processing of spectra.

Dissolution studies. – *In vitro* dissolution studies of PX, physical mixtures and freeze--dried complexes were performed by adding the solid systems, equivalent to 50 mg of

PX, to 500 mL of water thermostated at 37 ± 0.5 °C, and stirred at 50 rpm. At fixed time intervals, samples were withdrawn with a filter-syringe (0.45 μm) and assayed spectrophotometrically (Ultrospec Plus Spectrophotometer, Pharmacia LKB, Sweden) for the drug content at λ = 242 nm after suitable dilution with 0.01 mol L^{-1} methanolic HCl. The volume of the dissolution media was kept constant during the experiment.

Permeation studies. – Permeation of PX through the cellulose membrane (Medicell Dialysis Tubing MW CO 600, UK) from prepared solid systems was investigated using the Franz diffusion cell (Perme Gear, USA) with a diffusion area of 10.18 cm^2 and acceptor compartment volume of 17 mL, and compared to the permeation of the pure drug. The acceptor was filled with phosphate buffer solution (pH value 7.4), thermostated at 37 °C and continuously stirred at 600 rpm using a magnetic stirrer. Samples containing 0.02 g PX were dispersed in 1 mL of water and placed into the donor compartment. The amount of the drug permeated through the membrane was determined by removing aliquots at fixed time intervals from the acceptor compartment. The removed aliquot was replaced with the same volume of fresh buffer solution to obtain a constant volume of the acceptor solution during the experiment. The PX concentration in the samples was determined spectrophotometrically. Diffusion coefficient, D, was calculated using the equation:

$$D = \frac{B \times l_m}{C_I}$$

where B represents the slope of the drug release profile, l_m is the thickness of the cellulose membrane (l_m = 0.03 mm) and C_I is the initial concentration (mg mL^{-1}) of the drug in the donor compartment.

Gels preparation and characterization

Gels were prepared by dispersing HPMC (2%, *m*/*m*) in hot water (80 °C). The dispersions were mixed until cooling at room temperature and then PX or PX-CD complexes were added. Final PX concentration in gels was 1%. Prepared gels were stored at 4 °C for the following 24 h for complete swelling of the polymer and homogenization of the systems before characterization.

To characterize the prepared gels *in vitro*, gel permeation studies and rheological measurements were performed.

Permeation studies. – Permeation of PX from prepared gels through the cellulose membrane was investigated by filling the donor compartment of the Franz diffusion cell with 2 g of the prepared gels. All other experimental conditions were the same as described for permeation studies of solid systems.

Viscosity measurements. – Apparent viscosity of prepared gels was determined using a Brookfield Rheostress DV-III+ Rheometer (Brookfield Engineering Laboratories, UK). Measurements were performed in triplicate at 25 °C by using the spindle SC4. To determine the influence of shear stress applied on the microstructure of the gels, measurements were performed at a rotation speed of 1 and 10 rpm. Under the same conditions, the apparent viscosity of the control gel (2% HPMC dispersion in water) was examined.

RESULTS AND DISCUSSION

Phase solubility studies conducted for β-CD and RAMEB suggested formation of a PX-cyclodextrin inclusion complex with 1:1 stoichiometry (11). Equimolar PX-CDs solid complexes were prepared using freeze-drying. Evidence of the complexes formation was obtained by DSC, XRPD, FTIR and NIR. The content of PX in the prepared complexes was 22.6 and 19.9% for β-CD and RAMEB, respectively.

Differences in the thermal behaviour of PX, PX-cyclodextrins physical mixtures, and the corresponding inclusion complexes were evident. As shown in Fig. 1, PX exhibits a characteristic endothermic fusion peak at 200.8 °C and ΔH of 108 J g^{-1}, corresponding to the PX melting point and indicating that the drug is in a cubic crystal polymorphic form (12). Furthermore, β-CD and RAMEB show broad endothermic events in the range from 30 to 95 °C, which are related to the exit of adsorbed water, and small endo or exo effects at 210–325 °C due to thermal degradation. DSC thermograms of the physical mixture for PX and β-CD show the existence of the endothermic peak of piroxicam, indicating the absence of interaction between β-CD and PX. The PX peak in the physical mixture with RAMEB is reduced, indicating a more intense interaction of PX with RAMEB. The DSC thermograms of freeze-dried complexes show disappearance of the piroxicam endothermic peak at 200.8 °C. This could be attributed to the formation of an amorphous solid

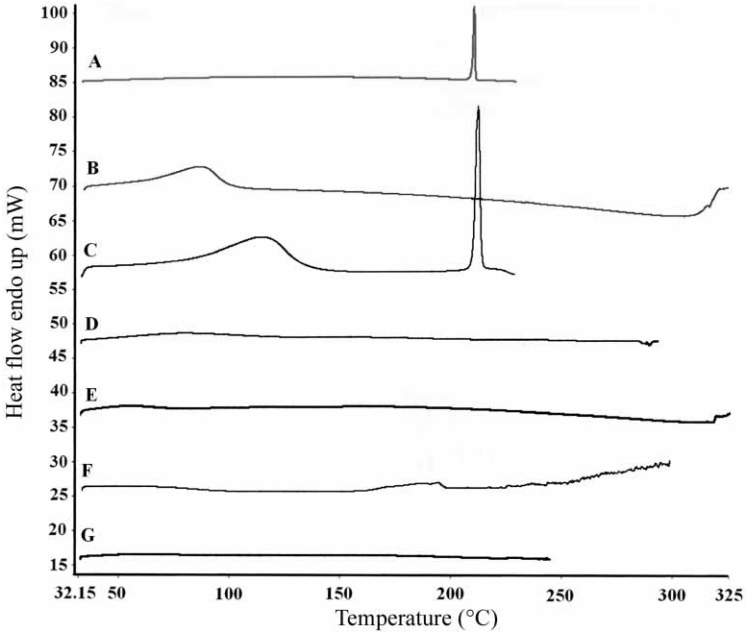

Fig. 1. DSC thermograms of PX (A), β-CD (B), PX and β-CD physical mixture (C), PX and β-CD freeze-dried complex (D), RAMEB (E), PX and RAMEB physical mixture (F), PX and RAMEB freeze-dried complex (G).

dispersion, molecular encapsulation of the drug into the CD cavity, or both. Although not unequivocally attributable to inclusion complexation, these phenomena are indicative of a strong interaction between PX, β-CD and RAMEB in the solid state (13).

XRPD patterns of PX, PX-cyclodextrin physical mixtures and the corresponding inclusion complexes are presented in Fig. 2. The presence of many different peaks in the PX diffraction pattern indicates that the drug is in crystalline form and the peaks of PX at 8.5° and 17.7° are selected as characteristic peaks in the mixture. The XRPD pattern of β-CD shows lower crystallinity while the data for RAMEB are completely diffused, indicating the presence of amorphous form. Diffraction patterns of physical mixtures show superposition of the spectra of each component, indicating the presence of PX in the crystalline state. In contrast, the diffraction patterns of freeze-dried complexes are completely diffuse and the disappearance of important PX crystalline peaks situated at 8.5° and 17.7° indicates the entirely amorphous nature of PX in these products. These results may be attributed to the interaction between PX and both CDs in the freeze-dried products, suggesting the presence of a new amorphous solid phase in the products, confirming the DSC observations.

More evidence of complex formation was obtained from FTIR studies, which investigated the functional groups of PX involved in the complexation (Fig. 3). FTIR spectra of PX show a band at 3339 cm^{-1}, which indicates that the drug is in the cubic polymor-

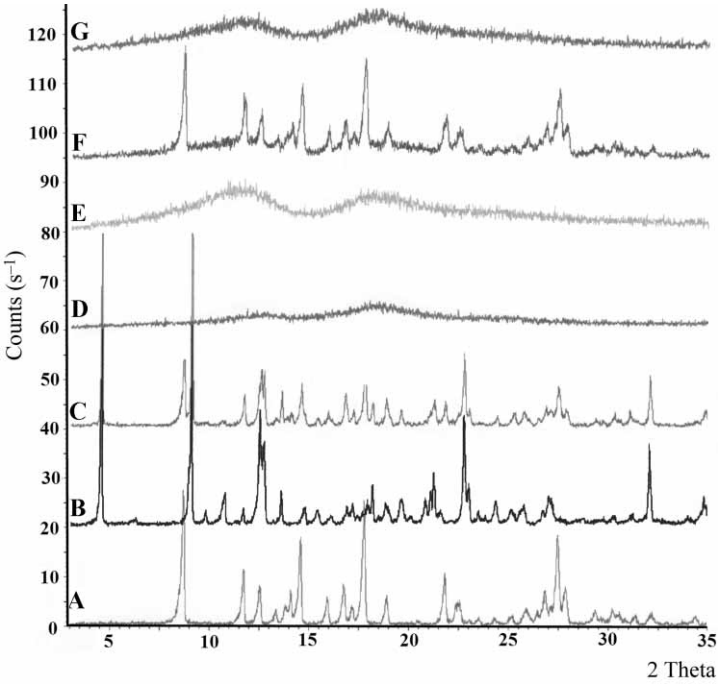

Fig. 2. XRPD patterns of PX (A), β-CD (B), PX and β-CD physical mixture (C), PX and β-CD freeze--dried complex (D), RAMEB (E), PX and RAMEB physical mixture (F), PX and RAMEB freeze-dried complex (G).

phic form. Other characteristic bands are attributed to the stretching of different group vibrations: 1630 cm^{-1} stretching of amide carbonyl, 1529 cm^{-1} stretching of the second amide band, 1435 cm^{-1} stretching of asymmetric methyl group, 1351 cm^{-1} stretching of symmetric methyl group, 1149 cm^{-1} stretching of $–SO_2$-N- group and 773 cm^{-1} as stretching of *ortho*-disubstitued phenyl (12). Patterns of physical mixtures show approximate superimposition of the patterns of the cyclodextrins and the drug. In the FTIR spectra of prepared complexes, PX bands are almost completely obscured by very intense and broad CD bands, which are hardly influenced by complex formation. Absorption bands of PX at 1630 and 1529 cm^{-1} experience a dramatic broadening in the spectra of the prepared freeze-dried complexes, and the peaks are shifted toward lower frequencies. This change is probably related to the formation of intramolecular hydrogen bonds between the guest and host molecules (14). It seems that when the carbonyl group is joined to a hydroxylic compound by hydrogen bonds, the stretching band is shifted to lower frequency due to the weakening of the carbonyl radical double bond (13).

NIR spectra of PX, β-CD, RAMEB, physical mixtures of the drug and the CDs as well as PX-CDs lyophilized complexes were collected in the diffuse reflectance mode (Fig. 4). PX spectrum shows two relatively sharp bands in the overtone region at 6000 cm^{-1} and 6500 cm^{-1} related to C-H and N-H vibrations, respectively. The hydroxyl groups of RAMEB give rise to wide bands in the NIR spectrum. Similar spectra of the RAMEB

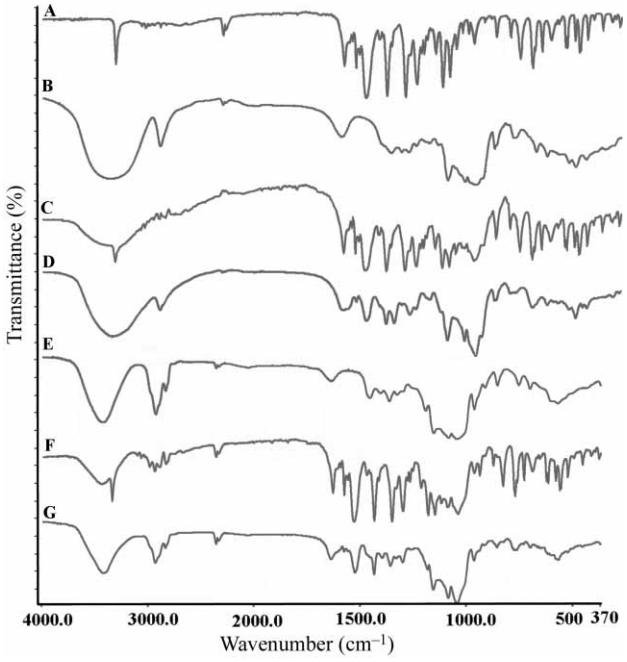

Fig. 3. FTIR spectra of PX (A), β-CD (B), PX and β-CD physical mixture (C), PX and β-CD freeze--dried complex (D), RAMEB (E), PX and RAMEB physical mixture (F), PX and RAMEB freeze-dried complex (G).

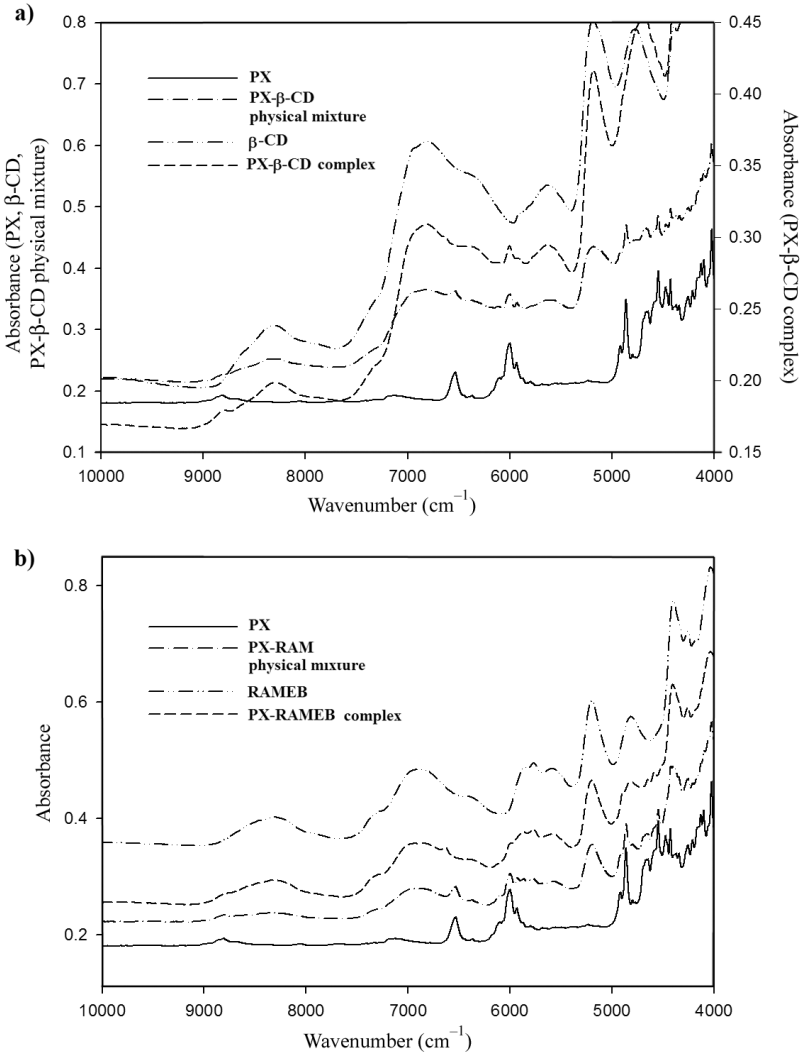

Fig. 4. NIR spectra of PX, CDs, physical mixtures and freeze-dried complexes for: a) β-CD, b) RAMEB.

and PX-RAMEB complexes were observed. Both spectra show wide bands belonging to hydroxyl groups, while significant shifting of PX bands in PX-RAMEB complex spectra, from 6532 to 6632 cm^{-1}, can be observed. This shifting reflects strong changes in the vibration energies of PX, which confirm its strong intramolecular bonding with RAMEB. It was previously described that PX makes very stable intramolecular hydrogen bonds, connecting the enol OH group with carbonyl oxygen, forming a six-membered ring (15). Taking into account these strong intramolecular interactions, we suggest that the bond-

ing of PX with RAMEB molecule could occur via hydrogen bonding of the hydroxyl group of CD with nitrogen unpaired electrons. This affects the N-H amide group vibration in such a way that a significant shift from 6532 cm^{-1} to 6632 cm^{-1} was observed. Some authors suggest that PX exists in a zwitter ionic form, where positive and negative charges are dislocated at the pyridinium nitrogen and the carbonyl oxygen, so the interaction of PX with CD could be attributed to electrostatic bonding, but also via hydrogen bonding (16, 17). Our finding confirmed a rather strong hydrogen interaction between a guest and a host molecule. Moreover, the position of the C-H vibration band (6000 cm^{-1}) does not change in the PX-RAMEB complex spectra, suggesting that there are no changes within the PX basic molecular structure during the complexation process. NIR spectra for the β-CD PX complex provide the same evidence for the complexation process as for the RAMEB complex. It was shown that the N-H band was shifted from 6532 cm^{-1} in PX spectra to 6624 cm^{-1} in β-CD PX complex spectra. The spectra of physical mixtures of PX and both cyclodextrins showed a plain superimposition of the drug and CD spectra, not indicating any interaction between PX and CDs.

PX release profiles from physical mixtures and PX-CDs complexes are represented in Fig. 5. It was shown that the dissolution of the drug from the complexes was very fast and completed within 10 min, reflecting improved aqueous solubility of the drug. Improvement of PX solubility obtained with physical mixtures compared to PX alone can be attributed to the local solubilization action of CD, operating in the microenvironment on the hydrodynamic layer surrounding the drug particles, which improves PX wettability and/or solubility. Also, the *in situ* formation of a readily soluble complex in the dissolution medium additionally contributed to the drug release from the prepared physical mixtures. Enhancement of the dissolution that occurred with freeze-dried complexes could be attributed to the complexation and to the high energetic amorphous state, as well as to the reduction in crystallinity following complexation, as confirmed by XRPD studies.

Various ointment bases containing PX were previously studied, and *in vitro* release of the drug was shown to be very low (less than 5%) (7). To improve the release rates, PX was complexed and incorporated into the hydrogel base. The permeation test was aimed to investigate the drug passage through a semipermeable membrane. Diffusion coefficients were determined from the steady-state region of the diffusion profiles shown as the cumulative amount of PX permeating the membrane against time (Table I). The effectiveness of cyclodextrin on drug diffusion was determined by comparing the diffusion coefficients (D) of PX in the presence and absence of CD, which was defined as the enhancement factor (EF).

Semipermeable cellulose membranes are highly permeable to many drugs and have a short lag time. These membranes are therefore useful for optimizing the cyclodextrins formulations for topical applications. Cyclodextrin will affect the flux through these membranes in the same way as in the case of skin. Permeation of PX from water and HPMC gels is shown in Figs. 6 and 7, respectively. Permeation of the drug from prepared systems in the donor compartment through a semipermeable membrane involves three consecutive processes: first, dissolution of the dispersed solid particles, then diffusion of the drug across the dissolution media or swollen polymer matrix, and finally its permeation through the membrane. All three processes make a contribution to the overall diffusion rate. The results showed that complexation increased the overall PX diffusion

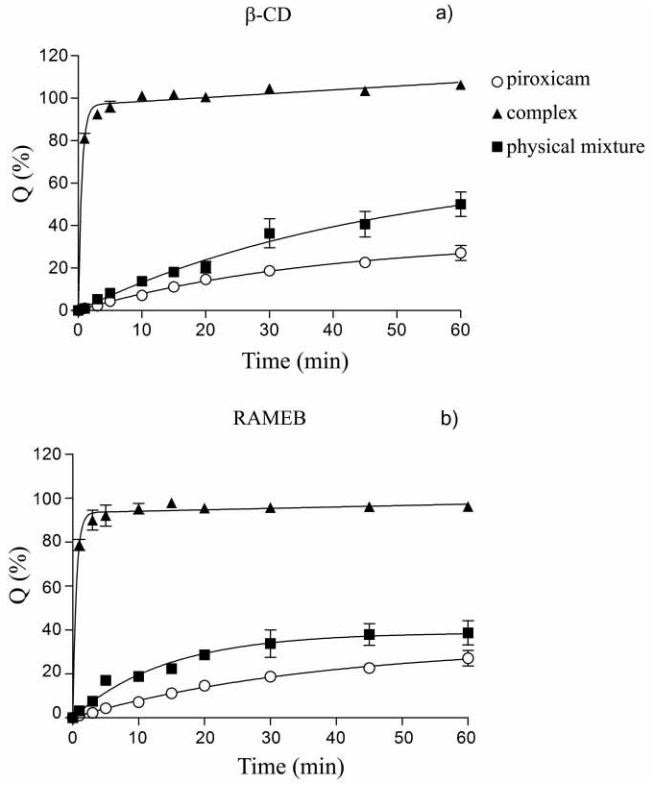

Fig. 5. Dissolution studies of PX, physical mixtures and freeze-dried complex in water at 37 °C (mean ± SD, $n = 5$) for: a) β-CD, b) RAMEB.

by increasing the amount of diffusible species in the donor phase by enhancing drug solubility. Though the complex could not penetrate, the drug in the complex was in rapid dynamic equilibrium with the free drug, thus continuously supplying PX molecules in a diffusible form to the membrane. Therefore, cyclodextrin complexation increased the PX concentration gradient over the membrane, which resulted in an increased PX diffusion

Table I. PX diffusion coefficient in phosphate buffer and in HPMC gels

System	D x 10^5 (cm^2 h^{-1})[a]	EF[b]	D x 10^5 (cm^2 h^{-1})[a]	EF[b]
	without HPMC		2% HPMC	
PX	7.03 ± 0.37	1	5.78 ± 0.32	1
PX-β-CD	123.09 ± 5.19	17.5	62.97 ± 3.21	10.9
PX-DM-β-CD	125.16 ± 11.12	17.8	87.45 ± 4.45	15.1

[a] Mean ± SD, $n = 5$.
[b] Enhancement factor.

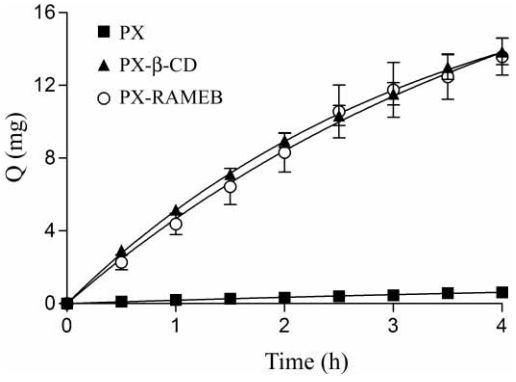

Fig. 6. Cumulative amount of diffused PX across semipermeable membrane from dispersions of the drug and complexes in water as a function of time (mean ± SD, $n = 5$).

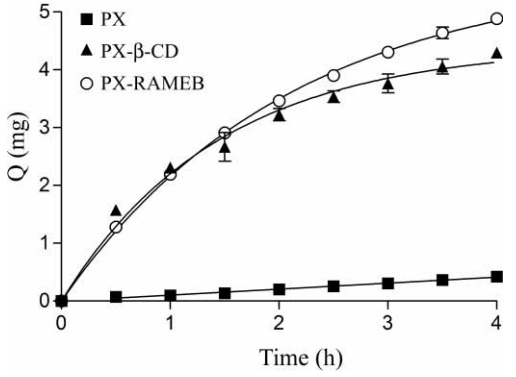

Fig. 7. Cumulative amount of diffused PX across semipermeable membrane from prepared gels as a function of time (mean ± SD, $n = 5$).

coefficient (Table I). The presence of a solid phase in the system (dispersion of drug/complex in water or gel) ensured constantly high drug thermodynamic activity on the membrane surface, replacing the drug molecules lost due to diffusion across the semipermeable membrane by dissolution of the solid phase. Cyclodextrins solubilize lipophilic drugs in the aqueous vehicle and deliver the drug molecules to the barrier surface where complex dissociation and drug permeation across semipermeable membrane occurred.

The presence of HPMC in gels retarded the release of PX compared to the data of PX permeation from water suspensions. This retarding effect could be explained by the slower diffusion of PX through the HPMC matrix layer. Swollen HPMC controlled the drug diffusion and consequently its release. Slower PX diffusion through the HPMC matrix was the rate limiting step in the overall diffusion process.

The stability constant values for β-CD and RAMEB PX complexes differed. RAMEB was shown to have better solubilizing and complexing properties for PX than β-CD, as it could be deduced from the higher stability constant values obtained for the complexes (11). Better complexing properties of RAMEB did not significantly affect drug diffusivity from water. The diffusion coefficient values for both cyclodextrins were almost the same. They differed only in the case of the drug permeation from HPMC gels, indicating some interactions of CDs with HPMC.

A number of papers have discussed the influence of formulation viscosity on drug release from topical formulations, demonstrating that an increase of viscosity would decrease the drug release rate (4, 8). Viscosity is a physical property, which at the molecular level can be rationalized in terms of an increasingly torturous route of migration through the gel, as a consequence of the reduced solvent content. The 2% HPMC water dispersion shows viscosity as declared by the manufacturer (Fig. 8), and the increase of rotation speed does not significantly change the viscosity of the sample, indicating formation of a stable gel structure. HPMC forms a physically bonded network by formation of the junction zones, which are responsible for the mechanical strength of the gel (18). The presence of the drug slightly reduced the gel viscosity and a more pronounced decrease of viscosity at higher rotation speed was observed. When CD complexes were incorporated in the gel, the viscosity of the samples dramatically decreased when higher rotation speed was applied (Fig. 8). The decrease in viscosity indicated the possibility of interaction between the complexes and HPMC chains, which could affect formation of the junction zones in the gel. CD inclusion complexes are known to interact with water-soluble polymers forming ternary complexes containing the drug molecule, CD and the polymer chain (19). Formation of the PX-CD-HPMC ternary complexes in the solution and in solid state was well characterized (11). In the ternary complex, the polymer partly or totally coats the inclusion complex, interacting both with the drug and the CD molecule through hydrogen bonds (20). This interaction can reduce the interaction between HPMC chains and therefore, at a higher rotation speed, the polymer chains are wholly disentangled and well aligned in the direction of the flow. The decrease in viscosity is more pronounced in the case of RAMEB. RAMEB is a chemically modified cyclodextrin with the degree of methylation of 1.8, and hence it is more lipophilic than the natural β-CD. Therefore, the higher decrease of viscosity in the case of RAMEB could be attributed to additional hydrophobic interaction between RAMEB and the polymer chains (21). Further experiments, such as viscoelastic measurements, are needed in order to investigate the mechanisms of interaction between the HPMC chains and PX complexes in gel samples.

Stability of the prepared gels was monitored during a period of 3 months and no sedimentation of the solid phase was observed. It seems that the amorphous state of complex particles and the viscosity of the gels were sufficient to stabilize the dispersion of solid particles in the gel systems.

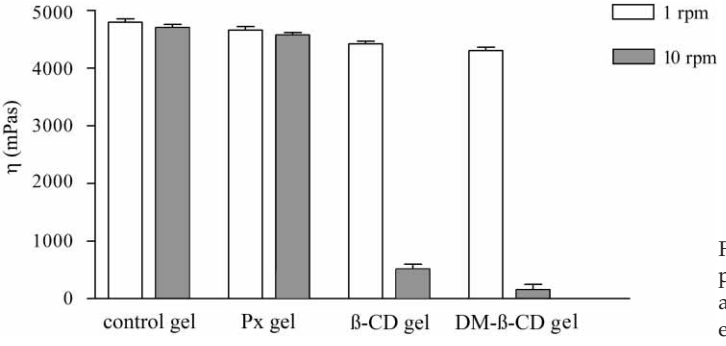

Fig. 8. Viscosity (η) of the prepared gels measured at different rotation speeds (mean ± SD, $n = 3$).

CONCLUSIONS

PX formed an inclusion complex with β-CD and RAMEB. Incorporation of the drug--cyclodextrin inclusion complex in hydrophilic gel effectively enhanced the drug permeation across semipermeable membrane. Interaction between CDs and HPMC chains changed the gel mechanical properties, so the nature of this interaction should be further investigated.

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S A Ž E T A K

Utjecaj kompleksacije piroksikama s ciklodekstrinima na oblikovanje gela

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Svrha rada bila je ispitati utjecaj kompleksacije piroksikama s ciklodekstrinima na oblikovanje pripravaka za topičku primjenu lijeka. Kompleksi piroksikama s β- i nasumično metiliranim β-ciklodekstrinom u krutom stanju pripremljeni su metodom sušenja smrzavanjem i karakterizirani su diferencijalnom pretražnom kalorimetrijom, difrakcijom X-zraka na prahu, infracrvenom spektroskopijom s Fourierovim transformacijama, te spektroskopijom u niskom infracrvenom području. Fizička smjesa lijeka s ciklodekstrinima karakterizirana je poboljšanom topljivošću u usporedbi sa čistim lijekom zbog stvaranja kompleksa *in situ*. Kompleksacija piroksikama sa ciklodekstrinima dodatno je poboljšala topljivost lijeka u liofiliziranom kompleksu. Ispitan je utjecaj ciklodekstrina na permeaciju lijekova iz vodenih disperzija i pripremljenih gelova s hidroksipropil metilcelulozom. Permeacija lijekova uključuje više uzastopnih procesa: otapanje krute faze, difuziju lijeka kroz izbubreni polimerni matriks, te difuziju lijeka kroz polupropusnu membranu. Kompleksacija piroksikama s ciklodekstrinima povećala je difuzibilnost lijeka uslijed porasta količine lijeka raspoloživog za difuziju. Difuzija lijeka kroz izbubreni polimerni matriks hidroksipropil metilceluloze pokazala se ključnim procesom koji određuje ukupnu difuziju lijeka. Interakcija hidrofilnog polimera s ciklodekstrinima utjecala je na fizikalno-kemijska svojstva gela, posebice na reološke parametere.

Ključne riječi: piroksikam, hidroksipropil metilceluloza, ciklodekstrin, topička primjena

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